From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 29 March 2001 (29.03.01)	
International application No. PCT/US00/16244	**Applicant's or agent's file reference** RTSP-0061
International filing date (day/month/year) 13 June 2000 (13.06.00)	**Priority date** (day/month/year) 25 June 1999 (25.06.99)
Applicant COWSERT, Lex, M.	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

17 January 2001 (17.01.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, ch min d s Col mbettes** **1211 G n va 20, Switz rland**	Authorized officer S. Mafla
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

US0016244

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/16244

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :C12N 15/86; C12Q 1/68; A61K 48/00; C07H 21/04, 21/02

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6, 91.1, 91.3, 325, 375; 536/23.1, 23.2, 24.5, 24.3, 24.31, 24.33; 514/44

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN, MEDLINE, BIOSIS, CAPLUS, LIFESCI, SEQUENCE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	MEIBNER ET AL. Retinoic acid-mediated decrease of G-alpha-S pro tein expression: Involvement of G-alpha-S in the differentiation of HL-60 myeloid cells. Experimental Cell Research. 1996, Vol. 225, No. 1, pages 112-121, especially page 115, figure2.	1, 2, 15 ------- 3-14, 16, 17
Y	GOETZL et al. Inhibition of human HL-60 cell responses to chemotactic factors by antisense messenger RNA depletion of G proteins. 14 January 1994, Vol. 269, No. 2, pages 809-812, see entire document.	1-17

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
13 JULY 2000	15 SEP 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer KAREN A. LACOURCIERE
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet) (July 1998)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/16244

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MILNER et al. . Selecting effective antisense reagents on combinatorial oligonucleotide arrays. Nature Biotechnology. June 1997, Vol. 15, pages 537-541, see entire document.	1-17
Y	JAMES, W. Towards gene-inhibition therapy: a review of progress and prospects in the field of antiviral antisense nucleic acids and ribozymes. Antiviral Chemistry and Chemotherapy. 1991, Vol. 2, No.4, pages 191-214, see especially pages 197-198.	1-17
Y	US 5,801,154 A (BARACCHINI et al.) 01 September 1998 (01/09/00), see entire document.	5-17
Y	KOZASA et al. Isolation and characterization of the human Gs alpha gene. Proc. Natl. Acad. Sci. USA. April 1998, Vol. 85, pages 2081-2085, see especially figure 2.	1-17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/16244

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 16 and 17
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 16 and 17 are directed to methods of treatment for a human being, the search has been carried out based on the alleged efects of the claimed compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all search claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payı of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report cc only those claims for which fees were paid, specifically claims Nos.:

4. [/] No required additional search fees were timely paid by the applicant. Consequently, this international search rep restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/16244

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

435/6, 91.1, 91.3, 325, 375; 536/23.1, 23.2, 24.5, 24.3, 24.31, 24.33; 514/44

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: JANE MASSEY LICATA
LAW OFFICES OF JANE MASSEY LICATA
66 E. MAIN STREET
MARLTON, NJ 08053

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing *(day/month/year)*	06 NOV 2001
Applicant's or agent's file reference RTSP-0061	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/US00/16244	13 JUNE 2000	25 JUNE 1999

Applicant
ISIS PHARMACEUTICALS, INC.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	KAREN A. LACOURCIERE Dorothia Faulkner for
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

Form PCT/IPEA/416 (July 1992) ★

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference RTSP-0061	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/16244	International filing date *(day/month/year)* 13 JUNE 2000	Priority date *(day/month/year)* 25 JUNE 1999
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant ISIS PHARMACEUTICALS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☒ Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☒ Certain documents cited

   VII ☐ Certain defects in the international application

   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17 JANUARY 2001	01 OCTOBER 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Dorthea Lawrence for KAREN A. LACOURCIERE Telephone No. (703) 308-0196

Form PCT/IPEA/409 (cover sheet) (July 1998) ★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/16244

I. Basis of the report

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-81, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of ____

[X] the claims:
pages 82-83, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE. filed with the demand
pages NONE, filed with the letter of ____

[X] the drawings:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of ____

[X] the sequence listing part of the description:
pages 1-24, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of ____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language ____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[X] contained in the international application in printed form.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [ ] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application.

☒ claims Nos. 16 and 17 (in part)

because:

☒ the said international application, or the said claim Nos. 16 and 17 (in part) relate to the following subject matter which

Claims 16 and 17 are directed to methods of treatment for a human being, which is comsidered to be non-statutory. The search of claims 16 and 17 has been carried out based on the alleged effects of the claimed compound/composition.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _ are so unclear that no meaningful opinion could be formed *(specify)*.

☐ the claims, or said claims Nos. _ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	3-14, 16 and 17	YES
	Claims	1, 2 and 15	NO
Inventive Step (IS)	Claims	none	YES
	Claims	1-17	NO
Industrial Applicability (IA)	Claims	1-17	YES
	Claims	none	NO

2. citations and explanations (Rule 70.7)

Claims 1, 2 and 15 lack novelty under PCT Article 33(2) as being anticipated by Meibner et al.

Meibner et al. disclsoe an antisense oligonucleotide 20 nucleotides long which is complementary to the 5' untranslated region of human Gs-alpha. Meibner et al. further disclose a method of inhibiting expression of human Gs-alpha in HL60 myeloid cells by contacting said cells in vitro with an antisense oligonucleotide expressed on a plasmid. Meibner et al. do not specif y whether their antisense molecule is targeted to the long or short form of Gs-alpha, in fig. 2 on page 115, an immunoblot indicates that treatment with their oligonucleotide results in a decrease of both forms. Therefore, MNeibner et al. anticipates claims 1, 2 and 15.

Claims 3-14, 16 and 17 lack an inventive step under PCT Article 33(3) as being obvious over Kozasa et al. in view of Meibner et al., Goetzl et al., Milner et al., James et al., and Baracchini et al.

Kozasa et al. teach the sequence of Human Gs-alpha gene.

Meibner et al. teach that inhibition of human Gs-alpha via an antisense molecule targeted to the 5'-UTR of huamn Gs-alpha will accelerate diferentiation of human myeloblastic leukemia cells.

Goetzl et al. teach inhibition of human Gs-alpha in cell culture via an expressed full length antisense targeted to human Gs-alpha mRNA.

Milner et al. and James et al. teach methods of making an screening antisense molecules against a target gene in any region, including the 5' or 3' untranslated region or the coding region.

Baracchini et al. teach 2'-O-methoxyethyl, 5-methylcytosine, chimeric oligonucleotides and modified internucleoside linkages, including phosphorothioate linkages, to incrase antisense stability, and antisense oligonucleotides 8-30 nucleotides in length.

It would have been obvious to make antisense against human Gs-alpha, since the prior art teaches the full length

(Continued on Supplemental Sheet.)

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication Date *(day/month/year)*	Filing Date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
US 6,110,664 A	29 AUGUST 2000	25 JUNE 1999	NONE

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(7): C12N 15/86; C12Q 1/68; A61K 48/00; C07H 21/04, 21/02 and US Cl.: 435/6, 91.1, 91.3, 325, 375; 536/23.1, 23.2, 24.5, 24.3, 24.31, 24.33; 514/44

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
gene sequence for human Gs-alpha. Additionally one would have been motivated to target human Gs-alpha because of its role in leukemia cell differentiation. It further would have been obvious to design such molecules of a length of 8-30 nucleotides because relatively short oligos are delivered into cells more efficiently and are easier to synthesize.

One would have expected to find antisense which inhibit human Gs-alpha as screening for such is routine and the prior art demonstrates inhibition of human Gs-alpha via one 20-mer antisense molecule and a full length antisense. It would have been further obvious to design such molecules with the modifications taught by Baracchini et al. for stability purposes. The claimed methods would have also been obvious because the methods of James et al. and Milner et al. provide for such inhibition and it is an obvious use of antisense designed to bind to human Gs-alpha.

---------- NEW CITATIONS ----------
NONE